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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/636,065	08/07/2003	Robert G. Korneluk	110-C1	1523

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EXAMINER

ZARA, JANE J

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 08/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/636,065

Applicant(s)

KORNELUK ET AL.

Examiner

Jane Zara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1-9 is/are allowed.
- 6) ☒ Claim(s) 10-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>5-9-05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office action is in response to the communication filed 6-6-06.

Claims 1-18 are pending in the instant application.

Election/Restrictions

Applicant's election with traverse of the oligonucleotide of SEQ ID NO. 29 in the reply filed on 6-6-06 is acknowledged. The traversal is on the ground(s) that the restriction requirement is improper because the MPEP states in its guidelines (sec 803.04 and sec 2434) that up to ten independent and distinct nucleotide sequences will be examined in most cases in a single application without restriction. Applicant is correct that the guidelines set forth in the MPEP at that time provided for possible examination of up to ten sequences in a single application. But, contrary to Applicant's assertions, the guidelines set forth in the MPEP at that time were suggested, and not mandatory. Furthermore, the data bases and art have expanded tremendously since the time these guidelines were written, rendering the searches required for proper examination much more burdensome. Applicant also argues that the antisense oligonucleotides claimed and disclosed in the instant specification are directed to either HIAP 1 or XIAP, are capable of use together, and therefore are not biologically or functionally distinct. Contrary to Applicant's assertions, the chemically distinct antisense are each directed to a different part of a target gene, and the ability of one oligonucleotide to provide or exert its effect biologically is not predictive of another oligonucleotide's ability to provide the same biological effect. Furthermore, since each

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oligonucleotide has a distinct nucleic acid sequence, the search of one oligonucleotide sequence is not coextensive with the search of a different and distinct oligonucleotide sequence, although, as Applicant suggests, the searches may overlap. For these reasons, the restriction requirement is maintained.

The requirement is still deemed proper and is therefore made FINAL.

The other SEQ ID Nos previously claimed are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6-6-06.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting expression of XIAP in vitro, does not reasonably provide enablement for methods of inhibiting expression of the XIAP gene in vivo, nor for methods of treating cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of treating any cancer comprising the administration by any means of SEQ ID NO. 29.

The state of the prior art and the predictability or unpredictability of the art.

Branch and Crooke teach that the *in vivo* (whole organism) application of molecules is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target molecules. (See entire text of A. Branch, Trends in Biochem. Sci., 23, 45-50, 1998; and S. Crooke, Antisense Res. & Application, Chapter 1, pages 1-50, ed. by S. Crooke, Springer-Verlag, especially pages 34-36).

Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired *in vivo* efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release... remains one of the major hurdles in the field." ((See Peracchi et al, Rev. Med. Virol., 14, pages 47-64, 2004, abstract on page 47 and text on page 51).

Cellular uptake by appropriate target cells is a rate limiting step that has yet to be overcome in achieving predictable clinical efficacy. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of small molecules *in vitro* and *in vivo* (see Agrawal et al, Molecular Med. Today, Vol. 6, pages 72-81, 2000, especially at pages 79-80; see Chirila et al, Biomaterials, Vol. 23, pages 321-342, 2002, especially pages 326-327 for a general review of the important

and inordinately difficult challenges of the delivery of therapeutic molecules to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. The specification teaches the in vitro inhibition of XIAP expression using antisense oligonucleotides. Applicants have not provided adequate guidance in the specification, however, of any in vivo inhibition of XIAP, nor any treatment of cancer in an organism using antisense. One skilled in the art would not accept on its face the examples given in the specification of the in vitro inhibition of expression of XIAP as being correlative or representative of the ability to successfully target and inhibit the expression of any nucleic acid encoding XIAP in a subject and further whereby treatment effects are provided for any cancer. There is a lack of guidance in the specification and an unpredictability associated with the successful targeting and delivery of biological agents to appropriate target cells in an organism, and further whereby treatments are provided for any cancer in a subject.

The breadth of the claims and the quantity of experimentation required. The claims are drawn to methods of treating a patient for any form of cancer comprising the administration by any means of the antisense oligonucleotide of SEQ ID No. 29. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues in an organism harboring XIAP, whereby the antisense oligonucleotide of SEQ ID NO. 29 is effectively delivered in adequate quantities to the target cells, and treatment effects are provided for any cancer in a

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subject comprising administration by any route of the antisense of SEQ ID NO. 29.

Since the specification fails to provide sufficient guidance for the methods claimed, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Allowable Subject Matter

SEQ ID No. 29 appears free of the prior art searched and of record.

Claims 1-9 are allowed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone

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number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
8-21-06

 TC 1600
JANE ZARA, PH.D.
PRIMARY EXAMINER